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(54) Title: METHOD OF PRODUCING PAROXETINE HYDROCHLORIDE

(57) Abstract

The present invention relates to a new process for preparing pharmaceutically active compounds and intermediates therefor. The (–) *trans* isomer of 4–(4'–fluorophenyl)–3–(3",4"–methylenedioxyphenoxymethyl)piperidine (paroxetine) is an important compound having antidepressant and anti–Parkinson properties. This compound is used in therapy as the hydrochloride salt to treat inter alia depression, obsessive compulsive disorder (OCD) and panic. There is described herein an improved process for its preparation which avoids the generation of impurities caused by the use of strong mineral acid to form the salt.

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METHOD OF PRODUCING PAROXETINE HYDROCHLORIDE

This invention is concerned with a new process for the preparation of hydrochloride salts of paroxetine.

Pharmaceutical products with antidepressant and anti-Parkinson properties are described in US-A-3912743 and US-A-4007196. An especially important compound among those disclosed is paroxetine, the (-) *trans* isomer of 4-(4'-fluorophenyl)-3-(3',4'-methylene-dioxyphenoxymethyl)-piperidine (see Example 2 of US-A-4007196). This compound is used in therapy as the hydrochloride salt to treat *inter alia* depression, obsessive compulsive disorder (OCD) and panic.

Paroxetine hydrochloride has been described in the literature as a crystalline hemihydrate (see EP-A-0223403 of Beecham Group) and as various crystalline anhydrate forms (see WO 96/24595 of SmithKline Beecham plc).

This invention aims to overcome disadvantages in the existing processes for preparation of paroxetine hydrochloride and so to provide alternative processes for its manufacture.

US-A-5672612 (Pentech) and EP-A-0810224 (Asahi Glass) describe the preparation of amorphous paroxetine hydrochloride by vacuum drying and spray drying.

In the literature, paroxetine hydrochloride is usually prepared by acidification of a solution of paroxetine base obtained as the final stage of a synthetic sequence. The preparation of paroxetine hydrochloride by addition of aqueous hydrochloric acid requires very acidic conditions for the formation of the salt from paroxetine base and this can result in the formation of unwanted impurities. The alternative use of hydrogen chloride gas on a large scale gives rise to high capital equipment costs and dangers of gas handling. The preparation of hydrogen chloride solutions in some solvents, for example ketones such as acetone and butanone, results in undesirable reactions, such as aldol condensation. WO 98/01424 (Richter Gedeon) describes procedures in which solutions of paroxetine acetate and tartrate salts are treated with aqueous solutions of sodium chloride or ammonium chloride to form paroxetine hydrochloride hemihydrate.

Procedures described in the literature for the preparation of solvated and anhydrous paroxetine hydrochloride require the use of anhydrous solvents such as acetone, ethyl acetate, toluene, n-butanol, chloroform, tetrahydrofuran, paropan-2-ol, and pyridine. Even if small amounts of water are present the anhydrate product is contaminated with paroxetine hydrochloride hemihydrate. WO 98/01424 does not describe the preparation

of anhydrous or solvated forms of paroxetine hydrochloride, and its procedures are unsuitable for operation under anhydrous conditions. Furthermore, amine hydrochlorides and paroxetine hydrochloride in anhydrous solutions form crystalline 1:1 mixed salts of the amine hydrochloride and paroxetine hydrochloride.

Surprisingly, we have discovered a process by which paroxetine hydrochloride can be prepared directly from paroxetine free base without the need for an intermediate salt, which is suitable for use under anhydrous conditions as well as aqueous conditions, and which is therefore suitable for the manufacture of anhydrous and solvated forms of paroxetine.

Hence, the present invention provides a process for the preparation of paroxetine hydrochloride in which a solution of paroxetine base or a salt other than the hydrochloride is contacted with an amine hydrochloride, and paroxetine hydrochloride is isolated as a solid, with the proviso that the use of ammonium chloride is excluded when treating paroxetine acetate or paroxetine tartrate in an aqueous system to obtain paroxetine hydrochloride for isolation as the hemihydrate.

Accordingly, in one aspect the present invention provides a process for the preparation of paroxetine hydrochloride anhydrate or solvate in which a solution of paroxetine base or a salt other than the hydrochloride is contacted with an amine hydrochloride, and paroxetine hydrochloride is isolated as an anhydrate or solvate, preferably in crystalline form.

In another aspect the present invention provides a process for the preparation of non-crystalline paroxetine hydrochloride in which a solution of paroxetine base or a salt other than the hydrochloride is contacted with an amine hydrochloride, and paroxetine hydrochloride is isolated in non-crystalline form.

In another aspect the present invention provides a process for the preparation of paroxetine hydrochloride hemihydrate in which a solution of paroxetine base is contacted with an amine hydrochloride in the presence of water, and paroxetine hydrochloride is isolated as the crystalline hemihydrate.

In a further aspect the present invention provides a process for the preparation of a paroxetine hydrochloride hemihydrate in which a solution of a paroxetine salt other than the hydrochloride, is contacted with an amine hydrochloride other than ammonium

chloride in the presence of water, and paroxetine hydrochloride is isolated as the crystalline hemihydrate.

In a yet further aspect the present invention provides a process for the preparation of a paroxetine hydrochloride hemihydrate in which a solution of a paroxetine salt other than the hydrochloride, acetate, or tartrate is contacted with ammonium chloride in the presence of water, and paroxetine hydrochloride is isolated as the crystalline hemihydrate.

This invention allows for the use of a mild, convenient, solid, cheap source of hydrogen chloride that can be conveniently added without expensive toxic gas handling facilities under mild conditions. The process can also be easily made anhydrous for the preparation of anhydrous forms of paroxetine hydrochloride; ambient temperature may be used and rigorous removal of water and complex solvent handling procedures are rendered unnecessary. The formation of paroxetine hydrochloride/amine hydrochloride crystalline 1:1 complexes is avoided by control of seeding or by avoiding excessively high concentrations.

The treatment with the amine hydrochloride preferably takes place under an atmosphere of inert gas, such as nitrogen or argon.

In the practice of this invention, the paroxetine hydrochloride may be isolated in non-crystalline form, for example by spray-drying or tray-drying, or as crystalline forms such as the hemihydrate, by crystallising from water or water-containing solutions, or as a crystalline anhydrate, or a crystalline solvate, such as the propan-2-ol, acetone, or toluene solvate, by crystallising from anhydrous solutions.

The amine hydrochloride is most conveniently commercially available material that can be used as supplied, but it may also be prepared *in situ*, for example by reaction of an amine with hydrogen chloride gas in a solvent. The amine hydrochloride may be used as a solid or in solution, and is preferably of low molecular weight. Suitable amine hydrochlorides are ammonium chloride, or based on primary alkylamines, preferably C_{1-6} alkyl, for example methylamine hydrochloride or ethylamine hydrochloride; primary aralkylamine, for example aryl C_{1-4} alkyl such as benzylamine hydrochloride; secondary alkylamine, preferably di-C_{1-4} alkyl for example dimethylamine hydrochloride or diethylamine hydrochloride; aromatic amine hydrochlorides, for example aniline hydrochloride; or heteroaromatic hydrochlorides, for example pyridine hydrochloride or collidine hydrochloride. Alternatively, high molecular weight polymeric amine

hydrochlorides may be used, for example polyvinylpyridine hydrochloride. It may be convenient to use a highly volatile amine salt such as methylamine hydrochloride, since purging the reaction mixture with an inert gas causes the free amine to be removed.

The isolation process may be by crystallisation and may include a conjugate amine removal step, for example by purging, filtering, or washing and drying. Alternatively a non-crystalline solid product may be isolated by spray drying, in which case it is particularly advantageous to use a highly volatile amine.

Preferably, an anhydrous solvent is used for the preparation of anhydrous forms of paroxetine hydrochloride, and water or a water-containing solvent mixture is used to prepare paroxetine hydrochloride hemihydrate. Suitable non-aqueous solvents include ethanol, propan-2-ol, butan-1-ol, toluene, acetone, ethyl acetate, and butanone.

Paroxetine base may be prepared *in situ*, for example by deprotection of (-)-trans-4-(4'-fluorophenyl)-3-(3'-4'-methylenedioxyphenoxymethyl-N-phenoxycarbonylpiperidine with potassium hydroxide in toluene followed by aqueous work up and phase separation. The resulting solution of base is conveniently dried by partial azeotropic distillation of the solvent, or the solvent may be removed completely by distillation and replaced by another solvent. The preparation of the base is described in Example 2 of US 4007196.

Suitable salts for starting materials include the maleic acid salt, also described in Example 2 of US 4007196. The acetate salt may also be used as a starting material. Procedures for forming salts are described in EP-A-0223403.

Paroxetine hydrochloride products of this invention, especially crystalline forms, may be formulated for therapy as described in EP-A-0223403 or WO 96/00477. The paroxetine hydrochloride is typically formulated with conventional excipients for tablet formation or with solid diluents for use as a powder fill for capsules.

The amount of paroxetine used is adjusted such that in a single unit dose there is a therapeutically effective amount of paroxetine. Preferably the unit dose contains from 10 to 100 mg paroxetine (measured in terms of the base). More preferably the amount of paroxetine in a unit dose is 10mg, 20mg, 30mg, 40mg or 50mg. The most preferred amount of paroxetine in a unit dose is 20mg.

Therapeutic uses of the paroxetine product of this invention include treatment of: alcoholism, anxiety, depression, obsessive compulsive disorder, panic disorder, chronic pain, obesity, senile dementia, migraine, bulimia, anorexia, social phobia, pre-menstrual syndrome (PMS), adolescent depression, trichotillomania, dysthymia, and substance abuse, referred to below as "the disorders".

Accordingly, the present invention also provides:

a pharmaceutical composition for treatment or prophylaxis of the disorders comprising paroxetine hydrochloride prepared by this invention and a pharmaceutically acceptable carrier;

the use of paroxetine hydrochloride prepared by the process of this invention to manufacture a medicament for the treatment or prophylaxis of the disorders; and

a method of treating the disorders that comprises administering an effective or prophylactic amount of paroxetine hydrochloride prepared by this invention to a person suffering from one or more of the disorders.

The invention is illustrated by the following Examples:

Example 1

A solution of paroxetine base (5 g) in propan-2-ol (50 ml) was treated with one equivalent of pyridine hydrochloride at room temperature under argon. The resulting solution was stirred rapidly at room temperature whereupon crystallisation occurred. After 20 minutes stirring was stopped, and the suspension diluted with propan-2-ol and filtered. The solid product was dried *in vacuo* over phosphorous pentoxide to give paroxetine hydrochloride propan-2-ol solvate (4.83 g).

Example 2

A solution of paroxetine hydrochloride base (8.7 g) in toluene (200 ml) was treated with wet pyridine hydrochloride (3.0 g) at room temperature. The resulting solution was stirred rapidly at room temperature for 1 hour whereupon crystallisation occurred. The solid was collected by filtration, washed with toluene, and dried *in vacuo* over phosphorous pentoxide to give paroxetine hydrochloride hemihydrate (4.69 g).

Example 3

A mixture of (-)-trans-4-(4'-fluorophenyl)-3-(3'-4'-methylenedioxyphenoxymethyl)-N-phenoxycarbonylpiperidine (25.0 g) in toluene (375 ml), and potassium hydroxide (22.5 g), was heated at reflux for 3 hours under nitrogen. The reaction mixture was cooled and stirred while water (250 ml) was added. The layers were separated and the organic layer dried by azeotropic distillation using a 'Dean and Stark' apparatus. Propan-2-ol (300 ml) was added and 300 ml of the solvent removed by distillation. This procedure was repeated twice more. The resulting solution was cooled and treated with pyridine hydrochloride (6.4 g). A thick white solid formed after approximately 30 minutes and the suspension was left to stand for 16 hours. Propan-2-ol (200 ml) was added to mobilise the mixture, then the product was collected by filtration and dried in a vacuum desiccator to give paroxetine hydrochloride propan-2-ol solvate (17.31 g) as a white crystalline solid (12 % propan-2-ol by weight).

Example 4

A solution of paroxetine base (5 g) in propan-2-ol (50 ml) was stirred with solid methylamine hydrochloride (1.0 g) at room temperature under nitrogen. The resulting solution was stirred rapidly at room temperature for 2 hours during which time a white precipitate formed. The precipitate was collected by filtration and dried *in vacuo* over phosphorous pentoxide to give paroxetine hydrochloride propan-2-ol solvate.

Example 5

A solution of paroxetine base (5 g) in butan-1-ol (50 ml) was stirred with pyridine hydrochloride (1.76 g) at room temperature under nitrogen. The resulting solution was stirred rapidly for 1 hour while a white solid precipitated. The solid was collected by filtration and dried *in vacuo* over phosphorous pentoxide to give paroxetine hydrochloride anhydrate Form C (2.32 g).

Example 6

A solution of paroxetine base (5 g) in propan-2-ol (50 ml) was stirred with ammonium chloride (1.0 g) at room temperature. A clear solution formed which was stirred rapidly at room temperature for 16 hours while a white crystalline solid precipitated. The solid was collected by filtration and dried *in vacuo* over phosphorous pentoxide to give paroxetine hydrochloride propan-2-ol solvate.

Example 7

A solution of paroxetine base (5 g) in propan-2-ol (50 ml) was treated with polyvinylpyridine hydrochloride (2.3 g) at 50°C. The reaction mixture was stirred for 30 minutes at the same temperature then filtered, and the filtrate cooled to room temperature. This solution was seeded with paroxetine hydrochloride propan-2-ol solvate, and stirred vigorously at room temperature for 1 hour. Crystallisation ensued, and the solid was collected by filtration and dried *in vacuo* over phosphorous pentoxide to give paroxetine hydrochloride propan-2-ol solvate.

Example 8

A solution of paroxetine base (4 g) in 2-butanone (40 ml) was treated with wet pyridine hydrochloride (1.40 g) at room temperature under argon. The resulting solution was stirred rapidly at room temperature for 16 hours while a white solid precipitated. This solid was collected by filtration, washed with butanone, and dried *in vacuo* over phosphorous pentoxide to give paroxetine hydrochloride hemihydrate (3.97 g).

Example 9

A solution of paroxetine base (5 g) in propan-2-ol (50 ml) was treated with benzylamine hydrochloride (2.10 g) at room temperature under argon. The resulting solution was stirred rapidly at room temperature for 2.5 hours while a white precipitate formed. The resulting solid was collected by filtration, washed with propan-2-ol, and dried *in vacuo* over phosphorous pentoxide to give paroxetine hydrochloride propan-2-ol solvate (2.84 g).

Example 10

A solution of paroxetine base in toluene (12 ml of a 0.42 g/ml solution) was diluted with propan-2-ol (40 ml), and aniline hydrochloride (1.96 g) was added with vigorous stirring. The reaction mixture was stirred for 4 hours and the solid that crystallised was isolated by filtration, washed with propan-2-ol, and dried *in vacuo* over phosphorous pentoxide to give paroxetine hydrochloride propan-2-ol solvate (4.96 g).

Example 11

Paroxetine free base (11.1 g) was dissolved in dry acetone (65 ml) under a nitrogen atmosphere and pyridine hydrochloride (4.1 g) added to the stirred solution.

Crystallization started after less than one minute and proceeded to afford a thick suspension. The resulting paroxetine hydrochloride acetone solvate was collected by vacuum filtration, washed with acetone and dried at 60°C under vacuum for 20 hours.

Example 12

A stirred mixture of N-phenoxycarbonyl paroxetine (19.4 g), potassium hydroxide (17.5 g) and toluene (300 ml) was heated to reflux under a nitrogen atmosphere for 3 hours. The mixture was cooled to room temperature, washed with water (200 ml) and the organic layer separated, dried over magnesium sulphate and concentrated to a total volume of 30ml. Dry acetone (50 ml) was added to the solution, under a nitrogen atmosphere and pyridine hydrochloride (5.0 g) added to the stirred solution. The mixture was stirred for 30 minutes and the product, paroxetine hydrochloride acetone solvate, collected by filtration, washed with acetone (20 ml) and dried under vacuum at 60°C for 20 hours.

Claims

1. A process for the preparation of paroxetine hydrochloride in which a solution of paroxetine base or a salt other than the hydrochloride is contacted with an amine hydrochloride, and paroxetine hydrochloride is isolated as a solid, with the proviso that the use of ammonium chloride is excluded when treating paroxetine acetate or paroxetine tartrate in an aqueous system to obtain paroxetine hydrochloride for isolation as the hemihydrate.

2. A process according to claim 1 in which the amine hydrochloride is added as a solid or as a solution.

3. A process according to claim 1 or 2 in which paroxetine hydrochloride is isolated in non-crystalline form, or as a crystalline hemihydrate, anhydrate, or solvate.

4. A process according to any one of claims 1 to 3 which is carried out under anhydrous conditions.

5. A process according to any one of claims 1 to 4 which is carried out under an atmosphere of inert gas.

6. A process according to any one of claims 1 to 5 in which the amine hydrochloride is selected from ammonium chloride, alkylamines, primary aralkylamines, secondary alkylamines, aromatic amine hydrochlorides, heteroaromatic hydrochlorides, and high molecular weight polymeric amine hydrochlorides.

7. A process according to claim 6 in which the amine hydrochloride is selected from methylamine hydrochloride, ethylamine hydrochloride, benzylamine hydrochloride, dimethylamine hydrochloride, diethylamine hydrochloride, aniline hydrochloride, pyridine hydrochloride, collidine hydrochloride, and polyvinylpyridine hydrochloride.

8. A process according to any one of claims 1 to 7 in which the paroxetine hydrochloride is isolated by crystallisation and the conjugate amine is removed by purging, filtering, or washing.

9. A process according to any one of claims 1 to 7 in which the amine hydrochloride is based on a volatile amine and the paroxetine hydrochloride is isolated by spray drying during which the conjugate amine is volatilised.

10. A process according to any one of claims 1 to 9 which is carried out under anhydrous conditions.

11. A process according to any one of claims 1 to 10 which is carried out in ethanol, propan-2-ol, butan-1-ol, toluene, acetone, ethyl acetate, or butanone.

12. A process for the preparation of paroxetine hydrochloride hemihydrate in which a solution of paroxetine base or a salt other than the hydrochloride is contacted with an amine hydrochloride other than ammonium chloride, and paroxetine hydrochloride is isolated as the crystalline hemihydrate.

13. A process for the preparation of paroxetine hydrochloride hemihydrate in which a solution of a paroxetine salt other than the hydrochloride, acetate or tartrate is contacted with an amine hydrochloride, and paroxetine hydrochloride is isolated as the crystalline hemihydrate.

14. A process for the preparation of a paroxetine hydrochloride anhydrate or solvate in which a solution of paroxetine base or a salt other than the hydrochloride is contacted with an amine hydrochloride, and paroxetine hydrochloride is isolated as an anhydrate or solvate, preferably in crystalline form.

15. A process for the preparation of non-crystalline paroxetine hydrochloride in which a solution of paroxetine base or a salt other than the hydrochloride is contacted with an amine hydrochloride, and paroxetine hydrochloride is isolated in non-crystalline form.

16. A pharmaceutical composition for treatment or prophylaxis of the disorders comprising paroxetine hydrochloride prepared by a process as claimed in any one of claims 1 to 15 and a pharmaceutically acceptable carrier.

17. Use of paroxetine hydrochloride prepared by a process as claimed in any one of claims 1 to 15 in the manufacture of a medicament for the treatment or prophylaxis of the disorders.

18. A method of treating the disorders that comprises administering an effective or prophylactic amount of paroxetine hydrochloride prepared by a process as claimed in any one of claims 1 to 15 to a person suffering from one or more of the disorders.

19. A process for the preparation of paroxetine hydrochloride substantially as described in any of examples 1 to 12.

INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/GB 99/03992

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D405/12 A61K31/4525

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 01424 A (BORZA ISTVAN ;CZIBULA LASZLO (HU); DOBAY LASZLO (HU); HARSANYI KAL) 15 January 1998 (1998-01-15) cited in the application examples 24,29	1,12,13, 16-19
A	EP 0 223 403 A (BEECHAM GROUP PLC) 27 May 1987 (1987-05-27) cited in the application examples	1,16-19
A	US 5 672 612 A (RONSEN BRUCE ET AL) 30 September 1997 (1997-09-30) cited in the application examples	1,15-19

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 January 2000	24/01/2000

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 99/03992

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 24595 A (SMITHKLINE BEECHAM PLC ;JACEWICZ VICTOR WITOLD (GB); WARD NEAL (GB) 15 August 1996 (1996-08-15) cited in the application example 4	1,14, 16-19
A	EP 0 810 224 A (ASAHI GLASS CO LTD) 3 December 1997 (1997-12-03) cited in the application examples	1,15-19

Form PCT ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/03992

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 18 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. nal Application No
PCT/GB 99/03992

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